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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/021,753	10/30/2001	Ken Fujise	UTSH:251US	6306

7590 05/12/2006

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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 05/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/021,753	FUJISE ET AL.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-89* is/are pending in the application.

4a) Of the above claim(s) *1-38 and 48-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-47 and 63-89* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Action is in response to the communication filed on 2/21/2006.

The amendment filed 2/21/2006 is acknowledged and has been entered.

Claims 1-89 are currently pending in the application and are addressed herein.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Claims 1-38, 48-62 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 6/1/2004.

Claims 39-47 and 63-89 are examined herein.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 39, 41, 63, 64, 84, 85 are rejected under 35 U.S.C. 102(b) as being anticipated by MacDonald et al. (Science 269:688-690, 1995; cited by Applicants in the 4/23/2002 IDS).

The instant claims are drawn to a method of identifying a modulator of a Fortilin polypeptide comprising: (a) contacting a Fortilin polypeptide with at least 70% of its amino acids

identical or functionally equivalent to SEQ ID NO:2 or that has at least 20 contiguous amino acids from SEQ ID NO:2 with a candidate substance; and (b) assaying whether the candidate substance modulates the Fortilin polypeptide (claim 39); wherein the assaying is done by determining whether the candidate substance specifically interacts with the Fortilin polypeptide (claim 41); wherein the candidate substance is a polypeptide (claim 63) wherein the polypeptide is an antibody (claim 64); wherein the Fortilin polypeptide is a mammalian Fortilin polypeptide (claim 84) wherein the mammalian Fortilin polypeptide is a human Fortilin polypeptide (claim 85).

It is noted that the limitation "modulates the Fortilin polypeptide" is very broad and encompasses any type of modulation. For instance, the mere binding of the candidate substance to the Fortilin polypeptide would constitute "modulating" the Fortilin polypeptide because the Fortilin polypeptide would be modulated to a complex comprising the substance bound to the Fortilin polypeptide.

MacDonald teaches an assay were an antibody was used in an immunoassay and was determined to specifically interact with the Fortilin polypeptide (e.g., see Figure 3 on page 689). MacDonald teaches that the antibody specifically binds to a mammalian Fortilin polypeptide that is a human Fortilin polypeptide (p23) that meets the structural limitations of the claims (e.g., see Figure 1 and Figure 3 on page 689). Accordingly, MacDonald anticipates the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 39-42, 44 and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over MacDonald et al. (Science 269:688-690, 1995; cited by Applicants in the 4/23/2002 IDS), and further in view of Gold et al. (U.S. Patent No. 5,270,163).

The instant claims are drawn to a method of identifying a modulator of a Fortilin polypeptide comprising: (a) contacting a Fortilin polypeptide with at least 70% of its amino acids identical or functionally equivalent to SEQ ID NO:2 or that has at least 20 contiguous amino acids from SEQ ID NO:2 with a candidate substance; and (b) assaying whether the candidate substance modulates the Fortilin polypeptide (claim 39); wherein the assaying compares the activity of Fortilin polypeptide in the presence and absence of the candidate substance (claim 40); wherein the assaying is done by determining whether the candidate substance specifically interacts with the Fortilin polypeptide (claim 41); wherein the modulator inhibits Fortilin (claim 42); wherein the modulator enhances Fortilin (claim 44) wherein the wherein the candidate substance is a nucleic acid (claim 65).

As indicated above, MacDonald teaches an assay were an antibody was used in an immunoassay and was determined to specifically interact with the Fortilin polypeptide (e.g., see Figure 3 on page 689). MacDonald teaches that the antibody specifically binds to a mammalian Fortilin polypeptide that is a human Fortilin polypeptide (p23) that meets the structural limitations of the claims (e.g., see Figure 1 and Figure 3 on page 689).

MacDonald also teaches that a polypeptide that meets the structural limitations of the instant claims induces the release of histamine from basophils (e.g., see Figure 2).

MacDonald does not teach that the activity of the polypeptide in the presence or absence of the candidate substance should be compared, that the modulator inhibits Fortilin, that the modulator enhances Fortilin, or that the candidate substance is a nucleic acid.

However, a method for identifying a nucleic acid modulator that specifically binds to and modulates the function of a polypeptide was known in the art. For instance, Gold et al. teaches a method known as SELEX (Systematic Evolution of Ligands by EXponential Enrichment) for identifying nucleic acid ligands that specifically bind to a target molecule, wherein the target molecule is a protein, and wherein the nucleic acid ligand can specifically inhibit or activate the function of the target protein (e.g., see abstract; column 1, lines 15-35; column 8, lines 40-67; column 9, lines 15-33; claims 1, 5, 7, 18). Furthermore, it would have been routine to one of ordinary skill in the art that in order to identify a substance which specifically binds to and modulates the function of a protein, the binding and function of the protein should be assayed in the presence and absence of the test substance.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the method taught by Gold et al. to identify nucleic acid molecules which specifically bind to and modulate the Histamine releasing function of the polypeptide(s) taught by MacDonald, including identifying nucleic acid inhibitors and activators of polypeptide(s) activity with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to identify modulators of the histamine releasing function the protein(s) taught by MacDonald because MacDonald teaches that histamine is involved in mediating the inflammatory response and can be useful in studying human allergic disease (e.g., see page 688, first paragraph of the article).

Claims 39-42, 44, and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over MacDonald et al. (Science 269:688-690, 1995; cited by Applicants in the 4/23/2002 IDS), and further in view of Dehlinger (WO 97/19749).

The instant claims are drawn to a method of identifying a modulator of a Fortilin polypeptide comprising: (a) contacting a Fortilin polypeptide with at least 70% of its amino acids identical or functionally equivalent to SEQ ID NO:2 or that has at least 20 contiguous amino acids from SEQ ID NO:2 with a candidate substance; and (b) assaying whether the candidate substance modulates the Fortilin polypeptide (claim 39); wherein the assaying compares the activity of Fortilin polypeptide in the presence and absence of the candidate substance (claim 40); wherein the assaying is done by determining whether the candidate substance specifically interacts with the Fortilin polypeptide (claim 41); wherein the modulator inhibits Fortilin (claim

42); wherein the modulator enhances Fortilin (claim 44) wherein the wherein the candidate substance is a small molecule (claim 66).

As indicated above, MacDonald teaches an assay were an antibody was used in an immunoassay and was determined to specifically interact with the Fortilin polypeptide (e.g., see Figure 3 on page 689). MacDonald teaches that the antibody specifically binds to a mammalian Fortilin polypeptide that is a human Fortilin polypeptide (p23) that meets the structural limitations of the claims (e.g., see Figure 1 and Figure 3 on page 689).

MacDonald also teaches that a polypeptide that meets the structural limitations of the instant claims induces the release of histamine from basophils (e.g., see Figure 2).

MacDonald does not teach that the activity of the polypeptide in the presence or absence of the candidate substance should be compared, that the modulator inhibits Fortilin, that the modulator enhances Fortilin, or that the candidate substance is a small molecule.

However, a method for identifying a small molecule modulator that specifically binds to and modulates the function of a polypeptide was known in the art. For instance, Dehlinger teaches a method for identifying one or more small molecules that specifically interact with a biological agent, such as a protein, using a combinatorial library of small molecules (e.g., see abstract; claim 19; page 6, lines 6-20; page 19, line 30 through page 20, line 36; etc.). Furthermore, it would have been routine to one of ordinary skill in the art that in order to identify a substance which specifically binds to and modulates the function of a protein, the binding and function of the protein should be assayed in the presence and absence of the test substance.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the method taught by Dehlinger to identify small molecules which specifically bind to the polypeptide(s) taught by MacDonald and to further test these small molecules for their ability to inhibit or activate the Histamine releasing function of the polypeptide as taught by MacDonald, with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to identify modulators of the histamine releasing function the protein(s) taught by MacDonald because MacDonald teaches that histamine is involved in mediating the inflammatory response and can be useful in studying human allergic disease (e.g., see page 688, first paragraph of the article).

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 39-47, 63-67, 84 and 85 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Method claims require an active or positive step that accomplishes the goals for the method which were stated in the method's preamble. Claims 39-47, 63-67, 84 and 85 lack such a step and are confusing because the additional method step(s) is not sufficiently set forth. While minute details are not required in method claims, at least the basic steps must be recited in a positive, active fashion. See Ex parte Erlich, 3 USPQ2d1011, p.1011 (Bd. Pat. App. Int. 1986). The specific problem with the instant claims is that the steps presented are simply a method of

identifying a modulator of a Fortilin polypeptide. There is no requirement or active or positive step in the claims that the method actually results in identification of the modulator. This is indefinite because it leaves the scope of the claim unclear as to whether or not the steps indicated as (a) and (b) in claim 39 are sufficient to identify the modulator.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39-47 and 63-89 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e. structure or other physical and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (See MPEP 2100-164).

In the instant case, the claims encompass methods for identifying modulators of "a Fortilin polypeptide" and encompass a Fortilin polypeptide that has "at least 70% of its amino acids identical or functionally equivalent to SEQ ID NO: 2 or that has at least 20 contiguous amino acids from SEQ ID NO: 2" (e.g., see claims 38 and 68). Therefore, the claims encompass a genus that encompasses an enormous number of different possible species. It is noted that the claims specifically indicate that the Fortilin polypeptides can be used to identify modulators of various Fortilin activities such as inhibition of apoptosis, binding to p53, binding to MCL1, cell cycle progression, etc. (e.g., see claims 43, 46, 47, 71-74). Therefore, the claims clearly encompass variants that must have the same function as human Fortilin (SEQ ID NO: 2) because the variants must have human Fortilin activity in order for the variants to be useful in methods of identifying modulators of human Fortilin activity. For instance, the Fortilin polypeptides that are used in the claimed methods to identify a modulator of p53-Fortilin interaction (e.g., claim 46) must possess the ability to interact with p53. The specification, however, has only disclosed one polypeptide that has all of the required functions to complete the claimed method: human Fortilin (SEQ ID NO: 2).

It is noted that the claims encompass a genus of polypeptides wherein 70% of the amino acids of the polypeptide are functionally equivalent to the amino acid sequence of SEQ ID NO: 2. This genus if polypeptides encompasses polypeptides that are completely different from SEQ ID NO: 2 (i.e., they are 0% identical to SEQ ID NO:2). Accordingly, the claims encompass methods which utilize variant polypeptides of SEQ ID NO: 2 (human Fortilin) wherein the variant polypeptides could be any variant of Fortilin that meet the broad structural limitations of the claims, including non-functional variants and variants that have a different function. As

such, the claims are drawn to the use of a polypeptide wherein the polypeptide can be any member of a huge genus of Fortilin polypeptides that meet the structural limitations of the claims. The specification has only described one species (SEQ ID NO: 2) of this vast genus that meets the structural limitations of the claims and which also have the same functions as human Fortilin. The specification does not disclose any other variants of Fortilin that maintain the anti-apoptotic activity, or that bind to p53 or MCL1, or that are involved in cell cycle progression; nor does the specification indicate which amino acids of Fortilin can be changed or deleted and result in a biologically active Fortilin variant. Furthermore, there is no structure function relationship described such that one of skill in the art would be able to clearly recognize any structural elements critical for Fortilin functions disclosed in the specification. Considering the huge number of possible variants encompassed by the claims and the limited guidance provided in the specification with respect to identifying the biologically active variants encompassed by the claims, it is the Examiner's position that the specification has not adequately described a sufficient number of "representative species" encompassed by the claims, as required.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states, "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) In this case, the specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). For the reasons indicated herein, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of Fortilin polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the

complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, the claims encompass a genus of "Fortilin" polypeptides that includes variants of human Fortilin which are structurally and functionally different from those explicitly described in the specification. The claimed genus encompasses all possible "Fortilin" polypeptide variants having at least 70% of its amino acids identical to or functionally equivalent to SEQ ID NO: 2 or that have at least 20 contiguous amino acids from SEQ ID NO: 2 (a huge number of possibilities). However, the specification has not adequately described a sufficient number of species or the critical functional elements common to the members of the genus. Therefore, the written description requirement has not been met and the rejection is proper.

It is noted that the specification does provide description of one specific sequence which has anti-apoptotic activity: the human Fortilin polypeptide that is SEQ ID NO: 2. It is noted that limiting the claims to the Fortilin polypeptide that is SEQ ID NO: 2 would obviate this rejection.

Additionally, claims 39-47 and 63-89 are also rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed methods wherein (1)

the Fortilin polypeptide that is contacted is isolated or in an isolated cell (see claims 39-47, 63-67, 84 and 85), (2) the recombinant cell that is contacted is an isolated cell, and (3) the Fortilin polypeptide has the amino acid sequence that is SEQ ID NO: 2; does not reasonably provide enablement for the full scope embraced by the claims. Specifically, the specification does not provide an enabling disclosure for performing the methods using a non-isolated cell, non-isolated Fortilin polypeptide (i.e., a cell or polypeptide that is in vivo), a non-isolated cell/polypeptide that is in a transgenic animal, or for the variant Fortilin polypeptides encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

> *Wands* states on page 1404,
> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claims are drawn to a screening method for identifying a modulator of a Fortilin polypeptide. The specification discloses that Fortilin polypeptide can be in a cell (e.g., see claim 67); and further indicates that the method can be performed in an animal including a transgenic animal (e.g., see page 107, lines 13-14). Accordingly, the invention is in a class of

invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The instant claims are very broad. For instance, claims 39-47, 63-66, 84 and 85 are drawn to "contacting a Fortilin polypeptide" with a candidate substance. Given the broadest reasonable interpretation, the phrase "contacting a Fortilin polypeptide" includes contacting a Fortilin polypeptide that is isolated as well as contacting a Fortilin polypeptide that is present in a cell. Claims 68-83 and 86-89 are drawn to contacting a candidate modulator with recombinant cell that expresses Fortilin. Given the broadest reasonable interpretation consistent with the specification, these claims encompass contacting a non-isolated recombinant cell such as a recombinant cell that is part of a transgenic animal. It is noted that page 107, lines 13-14 indicate that the "[a]ssays may be conducted in cell free systems, in isolated cells, or in organisms including transgenic animals" (Emphasis added). Furthermore, Dr. Rick Wetsel states in the Declaration filed 2/21/06 that the cells of the transgenic animals could be considered recombinant cells (see page 5 of the Declaration). Therefore, it is reasonable to interpret all of the examined claims as encompassing method steps that are performed on non-isolated cells, including cells of a transgenic animal. It is noted that the claims are not limited to using any particular type of animal, as such, the claims encompass using any transgenic animal (i.e., a transgenic animal of any species).

Furthermore, the claims encompass Fortilin polypeptides that have "at least 70% of [their] amino acids identical or functionally equivalent to SEQ ID NO: 2 or that has at least 20 contiguous amino acids from SEQ ID NO: 2" (e.g., see claims 38 and 68). Therefore, the claims

encompass methods that utilize any species of a genus of Fortilin polypeptides wherein the Fortilin polypeptide can be a variant or fragment of SEQ ID NO:2 that has a function different from the function of SEQ ID NO:2. It is noted that the genus of Fortilin polypeptides encompassed by the claims is enormous considering that the genus encompasses any polypeptide that has 70% of its amino acids functionally equivalent to SEQ ID NO: 2 as well as any polypeptide sequence that comprises 20 contiguous amino acids of SEQ ID NO: 2. The claims also specifically indicate that the methods encompass using any of the variant polypeptides to identify modulators that inhibit Fortilin, prevent Fortilin binding activity, enhance Fortilin, modulate cell cycle progression, prevent apoptosis, as well as using the variant polypeptides to determine whether a p53-Fortilin interaction is disrupted, an MCL1-Fortilin interaction is disrupted.

The unpredictability of the art and the state of the prior art

As indicated above, the claims encompass methods that utilize transgenic animals. In order to use the transgenic animals in the claimed methods, it is necessary to be able to make the transgenic animals that expresses the Fortilin polypeptide. However, the prior art teaches that making transgenic animals that express a functional transgene was unpredictable at the time the invention was made. For instance, the art of transgenic animals has for many years stated that the unpredictability lies with the site or sites of integration of the transgene into the target genome. Transgenic animals are regarded to have within their cells cellular mechanisms which prevent expression of the transgene, such as DNA methylation or deletion from the genome (**Kappel** et al (1992) Current Opinion in Biotechnology 3, 549, col. 2, parag. 2).

Furthermore, **Mullins et al.** states that not all animals express a transgene sufficiently expresses the transgene as the integration of a transgene into different species of animal has been reported to give divergent phenotypes (**Mullins et al.** (1993) Hypertension Vol. 22, page 631, col. 1, parag. 1, lines 14-17). Also, **Mullins et al.** (1996) teaches that "the use of nonmurine species for transgenesis will continue to reflect the suitability of a particular species for the specific questions being addressed, bearing in mind that a given construct may react very differently from one species to another." (**Mullins et al.** (1996) J. Clin. Invest. Vol. 97, page 1559, Summary).

Furthermore, well-regulated expression of the transgene is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues (**Cameron** (1997) Molec. Biol. Vol. 7, page 256, col. 1 -2, bridg. parag.). Factors influencing low expression, or the lack thereof, are not affected by copy number and such effects are seen in lines of transgenic mice made with the same construct (**Cameron** (1997), page 256, lines 3-9). These factors, thus, are copy number independent and integration site dependent, emphasizing the role the integration site plays on expression of the transgene (**Cameron** (1997), page 256, lines 10-13).

While, the intent is not to say that genetically modified animals can never be made, the intent is to provide art taught reasoning as to why the instant claims are not enabled to their full scope. Given unpredictable nature with respect to properly expressing a transgene in an animal as well as the variability of transgene expression in different animal species, particularly when taken with the lack of specific guidance in the specification, it would have required undue

experimentation to make the transgenic animals which have been engineered which are encompassed by the instant claims.

Additionally, the art recognizes that although structural similarity can serve to classify a protein as related to other known proteins, this classification is insufficient to establish a function or biological significance for the protein because ancient duplications and rearrangements of protein-coding segments have resulted in complex gene family relationships. Duplications can be tandem or dispersed and can involve entire coding regions or modules that correspond to folded protein domains. As a result, gene products may acquire new specificities, altered recognition properties, or modified functions. Extreme proliferation of some families within an organism, perhaps at the expense of other families, may correspond to functional innovations during evolution. See **Henikoff et al.** (Science 1997; previously cited). Accordingly, one skilled in the art would not accept mere homology as establishing a function of protein because gene products may acquire new specificities, altered recognition properties, or modified functions. Rather, homology complements experimental data accumulated for the homologous protein in understanding the homologous protein's biological role. Although, the presence of a protein module in a protein of interest adds potential insight into its function and guides experiments, insight into the biological function of a protein cannot be automated. However, homology can be used to guide further research. (See Henikoff, paragraph bridging pages 613-614, through page 614, paragraph bridging columns 1-2).

Furthermore, the art recognizes that a high degree of structural homology may not result in functional homology. **Witkowski et al.** (Biochemistry 1999; previously cited) teaches that one amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and

completely eliminates β-ketoacyl synthase activity. **Seffernick et al.** (J. Bacteriol., 2001; previously cited) teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Therefore, the claimed genus of "Fortilin" polypeptides has the potential of encompassing polypeptides that have different functions.

Considering the teachings of Henikoff et al., Witkowski et al., and Seffernick et al., it is unpredictable that any of the Fortilin variants encompassed by the claims would have human Fortilin function which is required to identify modulators of Fortilin activity, as specifically claimed (e.g., see claims 46, 47, 71-74, etc.).

Working Examples and Guidance in the Specification

The specification does not provide any working examples which indicate that a transgenic animal of any kind (i.e., of any species) which properly expresses a sufficient amount of Fortilin polypeptide to be useful in the claimed methods has been made. Furthermore, the specification has only provided general guidance with respect to making the transgenic animals encompassed by the claims (e.g.,. see pages 105-106). However, these general references do not overcome the art-recognized problems which render the making of transgenic animals that properly express a sufficient level of a transgenic protein unpredictable.

Additionally, there are no techniques which have been disclosed in the specification or found in the relevant art which teach how to predictably perform the claimed assays on a non-isolated cell (e.g., an in vivo cell).

The specification discloses 7 specific sequence homologs of SEQ ID NO: 2 that meet the structural limitations of the claims (e.g., see Figure 1). The specification asserts that there are 3

domains of Fortilin, but does not disclose the specific function of each of the domains. The specification has disclosed a specific function for SEQ ID NO:2 as inhibiting p53-mediated apoptosis (e.g., Figure 5) and specifically binds to MCL-1 and p53 (e.g., see Examples 1 and 2). The specification does not disclose that any of the Fortilin homologs that are different from human Fortilin have the same function as human Fortilin and the categorization of the other polypeptides appears to be based solely on sequence homology.

Quantity of Experimentation

Considering the breadth of the claims, especially with respect to the number of different species of transgenic animals encompassed by the claims, and further considering that the prior art teaches that making transgenic animals is an unpredictable endeavor, the amount of additional experimentation required to be able to make the transgenic animals encompassed by the claims is enormous. For instance, additional experimentation would be required to show that a transgenic animal that properly expresses a sufficient amount of transgenic Fortilin polypeptide could be predictably made. Once this was completed, additional experimentation would be required to show that the different species of transgenic animals could be made that properly express a sufficient amounts of transgenic Fortilin polypeptide. Considering that the art teaches that different species of animals can express that same polypeptide differently (e.g., see Mullins 1996 as indicates above), the amount of additional experimentation required to show that the different species of transgenic animals encompassed by the claims could be predictably made is also enormous.

Furthermore, considering the breadth of the claims with respect to the number of different Fortilin polypeptides encompassed by the claims and considering that the specification has not

adequately described the structural elements that are critical to function, additional experimentation would be required in order identify which variants of SEQ ID NO: 2 would be useful in the claimed methods and which ones would not be useful. That is, additional experimentation would be required in order to determine which variants encompassed by the claims could be used to identify a modulator of Fortilin activity and which ones would not be useful.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the nature of the invention, the breadth of the claims, the unpredictable nature of the invention as recognized in the prior art, the lack of working examples and the limited guidance provided by the specification, as well as the high degree of skill required to practice the invention, it is concluded that the specification does not provide an enabling disclosure commensurate in scope with instant claims. Therefore, additional experimentation is required before one of skill in the art could predictably make and use the claimed invention to its full scope. The amount of additional experimentation required to perform the broadly claimed invention is undue.

Response to Arguments

Applicant's arguments filed 2/21/2006 have been fully considered.

The Declaration of Dr. Rick A. Wetsel under 37 CFR 1.132 filed 2/21/2006 is sufficient to overcome the rejection of claims 68-83 and 85-88 under 35 U.S.C. 112, 1st paragraph (new

matter) as the declaration has pointed to the specific passages of the specification that provide support for the limitations.

Applicants arguments with respect to the written description rejection can be summarized as follows: (1) the Examiner relies on an argument of structure and function yet has not explained how this is relevant to the claimed invention; (2) A representative number of species has been described; (3) the present scenario is distinguishable from cases liker *Fiers v. Revel,* 25 USPQ2d 1 601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharm. Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991) because the present claims recite a specific structure (reference to SEQ ID NO:2) and are not characterized in terms of function only; and (4) the Examiner has not set forth why Applicants need to provide a reasonable number of representative species in the context of the claimed invention.

With respect to argument (1), the instant rejection sets forth why function is relevant to the claimed invention: the polypeptides that are used to identify modulators of Fortilin activity (as explicitly claimed, for example in claims 46-47 and 71-74) must have Fortilin activity. With respect to argument (2), since the variant polypeptides encompassed by the claims must have Fortilin activity, the specification has not described a representative number of species because only one species that has the required functions has been described: human Fortilin (SEQ ID NO: 2). With respect to argument (3), *Fiers v. Revel* has been removed from the instant rejection. With respect to *Amgen Inc. v. Chugai Pharm. Co. Ltd,* as it applies to the instant case, Applicants are reminded that MPEP § 2163 states:

> "Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was 'ready for patenting' such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to

> show that the applicant was in possession of the claimed invention. See, e.g., Pfaff v. Wells Elecs., Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991)."

In the instant case, the invention is not "ready for patenting" because the description of the instant application is not sufficient to show that the applicant was in possession of the claimed invention, which includes variants of SEQ ID NO: 2 which have human Fortilin activity. Therefore, based on MPEP § 2163, the Amgen case is appropriate. With respect to argument (4), Applicants need to provide a reasonable number of representative species in the context of the claimed invention because with a reasonable number of representative species, Applicants have not shown that they were in possession of the variants polypeptides that have the Fortilin activities required for the claimed methods.

Applicants also argue that it appears that the references relied upon in the written description rejection (Henikoff et al., Witkowski et al., and Seffernick et al.) would be better applied under an enablement rejection, but there is no enablement rejection of record.

In response, the claims are now also rejected under 35 USC 112, 1st paragraph for not being enabled for their full scope, and the indicated references have been incorporated into the enablement rejection and removed from the written description rejection.

Applicants also argue that the written description rejection is inappropriate because there is no requirement in the claims that the Fortilin polypeptides are biologically active or that they have a certain function.

In response, although it is acknowledged that there is no specific recitation in the claims that the polypeptides have a particular function, the polypeptides must have human Fortilin

activity in order for to identify modulators of the specifically claimed Fortilin activities such as p53 binding, MCL1 binding, inhibition of apoptosis, and cell cycle regulation.

The Applicants argue that a similar written description rejection was overturned by the BPAI in *Ex Parte Friedberg,* which Applicants assert has been submitted as Exhibit 1. It is noted that Exhibit 1 was not received by the Office. However, the Examiner was able to independently locate and review *Ex Parte Friedberg.* It is noted that *Ex Parte Friedberg* is neither written for publication or binding precedent. Furthermore each case is decided on its own merits and the fact pattern in *Ex Parte Friedberg* is different from the instant fact pattern. For instance, the polypeptides in *Ex Parte Friedberg* are drawn to pol K polypeptides which are polymerase enzymes while the instant claims are drawn to Fortilin polypeptides which are not polymerase enzymes and the description requirement for the enzymes in Friedberg are different from the description requirement of the instant case.

With respect to the new matter rejection, it is noted that the rejection has been withdrawn.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JON ANGELL
PATENT EXAMINER